HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLULAVAL QUADRIVALENT safely and effectively. See full prescribing information for FLULAVAL QUADRIVALENT.

FLULAVAL QUADRIVALENT (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2013-2014 Formula
Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------

FLULAVAL QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT is approved for use in persons 3 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
3 through 8 years of age	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each) (2.1)
9 years of age and older	Not applicable	One 0.5-mL dose (2.1)

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection in 5-mL multi-dose vials containing ten 0.5-mL doses. (3)

----------CONTRAINDICATIONS----------

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (4, 11)

---------- WARNINGS AND PRECAUTIONS ----------

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL QUADRIVALENT. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

---------- ADVERSE REACTIONS ----------

- In adults, the most common (≥10%) solicited local adverse reaction was pain (60%); most common solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). (6.1)
- In children 3 through 17 years of age, the most common (≥10%) solicited local adverse reaction was pain (65%). (6.1)
- In children 3 through 4 years of age, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). (6.1)
- In children 5 through 17 years of age, the most common (≥10%) solicited systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of FLULAVAL QUADRIVALENT have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLULAVAL QUADRIVALENT while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Geriatric Use: Antibody responses were lower in geriatric subjects who received FLULAVAL QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL® QUADRIVALENT is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT is approved for use in persons 3 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLULAVAL QUADRIVALENT are presented in Table 1.

Table 1. FLULAVAL QUADRIVALENT: Dosing

Age	Vaccination Status	Dose and Schedule
3 through 8 years of age	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each)
9 years of age and older	Not applicable	One 0.5-mL dose

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Use a sterile needle and sterile syringe to withdraw the 0.5-mL dose from the multi-dose vial and administer intramuscularly. A sterile syringe with a needle bore no larger than 23 gauge is recommended for administration. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

The preferred site for intramuscular injection is the deltoid muscle of the upper arm. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Between uses, return the multi-dose vial to the recommended storage conditions, between

2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-dose vial, and any residual contents, should be discarded after 28 days.

Do not administer this product intravenously, intradermally, or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL QUADRIVALENT is a suspension for injection available in 5-mL multi-dose vials containing ten 0.5-mL doses.

4 CONTRAINDICATIONS

Do not administer FLULAVAL QUADRIVALENT to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case/one million persons vaccinated.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLULAVAL QUADRIVALENT.

5.4 Altered Immunocompetence

If FLULAVAL QUADRIVALENT is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL QUADRIVALENT may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL QUADRIVALENT should be given

with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In adults who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (60%); the most common (≥10%) solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%).

In children 3 through 17 years of age who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (65%). In children 3 through 4 years of age, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children 5 through 17 years of age, the most common (≥10%) systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of FLULAVAL QUADRIVALENT could reveal adverse reactions not observed in clinical trials.

FLULAVAL QUADRIVALENT has been administered to 1,384 adults 18 years of age and older and 3,516 pediatric subjects 3 through 17 years of age in 4 clinical trials.

FLULAVAL QUADRIVALENT in Adults: Study 1 was a randomized, double-blind, active-controlled, safety and immunogenicity study. In this study, subjects received FLULAVAL QUADRIVALENT (N = 1,272), or one of two formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, N = 213 or TIV-2, N = 218), each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was 18 years of age and older (mean age 50 years) and 61% were female; 61% of subjects were White, 3% were Black, 1% were Asian, and 35% were of other racial/ethnic groups. Solicited adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in adults are shown in Table 2.

Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events Within 7 Days[a] of Vaccination in Adults 18 Years of Age and Older[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT[c] N = 1,260 %	Trivalent Influenza Vaccine (TIV)	
		TIV-1 (B Victoria)[d] N = 208 %	TIV-2 (B Yamagata)[e] N = 216 %
Local Adverse Reactions			
Pain	60	45	41
Swelling	3	1	4
Redness	2	3	1
Systemic Adverse Events			
Muscle aches	26	25	19
Headache	22	20	23
Fatigue	22	22	17
Arthralgia	15	17	15
Gastrointestinal symptoms[f]	9	10	7
Shivering	9	8	6
Fever ≥100.4°F (38.0°C)	2	1	1

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Study 1: NCT01196975.

[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

[d] Contained two A strains and a B strain of Victoria lineage.

[e] Contained the same two A strains as FLULAVAL and a B strain of Yamagata lineage.

[f] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited adverse events occurring within 21 days of vaccination were reported in 19%, 23%, and 23% of subjects who received FLULAVAL QUADRIVALENT (N = 1,272), TIV-1 (B Victoria) (N = 213), or TIV-2 (B Yamagata) (N = 218), respectively. The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included nasopharyngitis, upper respiratory tract infection, headache, cough and oropharyngeal pain. Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

FLULAVAL QUADRIVALENT in Children: Study 2 was a randomized, double-blind, active-controlled study. In this study, subjects received FLULAVAL QUADRIVALENT

(N = 932), or one of two formulations of a comparator trivalent influenza vaccine [FLUARIX® (Influenza Virus Vaccine), TIV-1, N = 929 or TIV-2, N = 932], each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was 3 through 17 years of age (mean age 9 years) and 53% were male; 65% were White, 13% were Asian, 9% were Black, and 13% were of other racial/ethnic groups. Children 3 through 8 years of age with no history of influenza vaccination received 2 doses approximately 28 days apart. Children 3 through 8 years of age with a history of influenza vaccination and children 9 years of age and older received one dose. Solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in children are shown in Table 3.

Table 3. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events Within 7 Days[a] of First Vaccination in Children 3 Through 17 Years of Age[b] (Total Vaccinated Cohort)

		Trivalent Influenza Vaccine (TIV)	
	FLULAVAL QUADRIVALENT[c] %	**TIV-1 (B Victoria)[d] %**	**TIV-2 (B Yamagata)[e] %**
	3 Through 17 Years of Age		
Local Adverse Reactions	**N = 913**	**N = 911**	**N = 915**
Pain	65	55	56
Swelling	6	3	4
Redness	5	3	4
	3 Through 4 Years of Age		
Systemic Adverse Events	**N = 185**	**N = 187**	**N = 189**
Irritability	26	17	22
Drowsiness	21	20	23
Loss of appetite	17	16	13
Fever ≥100.4°F (38.0°C)	5	6	4
	5 Through 17 Years of Age		
Systemic Adverse Events	**N = 727**	**N = 724**	**N = 725**
Muscle aches	29	25	25
Fatigue	22	24	23
Headache	22	22	20
Arthralgia	13	12	11
Gastrointestinal symptoms[f]	10	10	9
Shivering	7	7	7
Fever ≥100.4°F (38.0°C)	2	4	3

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were

available.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Study 2: NCT01198756.

[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

[d] Contained two A strains and a B strain of Victoria lineage.

[e] Contained the same two A strains as FLUARIX and a B strain of Yamagata lineage.

[f] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 30%, 31% and 30% of subjects who received FLULAVAL QUADRIVALENT (N = 932), FLUARIX TIV-1 (B Victoria) (N = 929), or TIV-2 (B Yamagata) (N = 932), respectively. The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse events occurring within 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of subjects who received FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

Study 3 was a randomized, observer-blind, non-influenza vaccine-controlled study evaluating the efficacy of FLULAVAL QUADRIVALENT. The study included subjects 3 through 8 years of age who received FLULAVAL QUADRIVALENT (N = 2,584) or HAVRIX® (Hepatitis A Vaccine) (N = 2,584), as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were White, and 35% were of other racial/ethnic groups. The mean age of subjects was 5 years. Solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in children are shown in Table 4.

Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events Within 7 Days[a] of First Vaccination in Children 3 Through 8 Years of Age[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT %	HAVRIX[c] %
	3 Through 8 Years of Age	
Local Adverse Reactions	**N = 2,546**	**N = 2,551**
Pain	39	28
Swelling	1	0.3
Redness	0.4	0.2
	3 Through 4 Years of Age	
Systemic Adverse Events	**N = 898**	**N = 895**
Loss of appetite	9	8
Irritability	8	8
Drowsiness	8	7
Fever ≥100.4°F (38.0°C)	4	4
	5 Through 8 Years of Age	
Systemic Adverse Events	**N = 1,648**	**N = 1,654**
Muscle aches	12	10
Headache	11	11
Fatigue	8	7
Arthralgia	6	5
Gastrointestinal symptoms[d]	6	6
Shivering	3	3
Fever ≥100.4°F (38.0°C)	3	3

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Study 3: NCT01218308.

[c] Hepatitis A Vaccine used as a control vaccine.

[d] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLULAVAL QUADRIVALENT or HAVRIX, the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

The frequency of unsolicited adverse events occurring within 28 days of vaccination was similar in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper respiratory tract infection, varicella, cough, and rhinorrhea. Serious adverse events occurring

within 28 days of any vaccination were reported in 0.7% of subjects who received FLULAVAL QUADRIVALENT and in 0.2% of subjects who received HAVRIX.

6.2 Postmarketing Experience

There are no postmarketing data available for FLULAVAL QUADRIVALENT. The following adverse events have been spontaneously reported during postapproval use of FLULAVAL (trivalent influenza vaccine). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence rate or establish a causal relationship to the vaccine. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

Blood and Lymphatic System Disorders: Lymphadenopathy

Eye Disorders: Eye pain, photophobia

Gastrointestinal Disorders: Dysphagia, vomiting

General Disorders and Administration Site Conditions: Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess

Immune System Disorders: Allergic reactions including anaphylaxis, angioedema

Infections and Infestations: Rhinitis, laryngitis, cellulitis

Musculoskeletal and Connective Tissue Disorders: Muscle weakness, arthritis

Nervous System Disorders: Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis

Psychiatric Disorders: Insomnia

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, dysphonia, bronchospasm, throat tightness

Skin and Subcutaneous Tissue Disorders: Urticaria, localized or generalized rash, pruritus, sweating

Vascular Disorders: Flushing, pallor

7 DRUG INTERACTIONS

7.1 Concomitant Administration With Other Vaccines

FLULAVAL QUADRIVALENT should not be mixed with any other vaccine in the same syringe or vial.

There are insufficient data to assess the concomitant administration of FLULAVAL QUADRIVALENT with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the

immune response to FLULAVAL QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

A reproductive and developmental toxicity study has been performed in female rats at a dose 80-fold the human dose (on a mg/kg basis) and showed no evidence of impaired female fertility or harm to the fetus due to FLULAVAL QUADRIVALENT. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, FLULAVAL QUADRIVALENT should be given to a pregnant woman only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLULAVAL QUADRIVALENT on embryo-fetal and pre-weaning development was evaluated in rats. Animals were administered FLULAVAL QUADRIVALENT by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation days 3, 8, 11, and 15), and during lactation (day 7), 0.2 mL/dose/rat (80-fold higher than the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

Pregnancy Registry: GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with FLULAVAL QUADRIVALENT during pregnancy. Women who receive FLULAVAL QUADRIVALENT during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

8.3 Nursing Mothers

It is not known whether FLULAVAL QUADRIVALENT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLULAVAL QUADRIVALENT is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL QUADRIVALENT in children younger than 3 years of age have not been established.

Safety and immunogenicity of FLULAVAL QUADRIVALENT in children 3 through 17 years of age have been evaluated *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

8.5 Geriatric Use

In a randomized, double-blind, active-controlled study, immunogenicity and safety were evaluated in a cohort of subjects 65 years of age and older who received FLULAVAL QUADRIVALENT (N = 397); approximately one-third of these subjects were 75 years of age and older. In subjects 65 years of age and older, the geometric mean antibody titers post-vaccination and seroconversion rates were lower than in younger subjects (18 to 64 years of age) and the frequencies of solicited and unsolicited adverse events were generally lower than in

younger subjects *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

11 DESCRIPTION

FLULAVAL QUADRIVALENT, Influenza Virus Vaccine, for intramuscular injection, is a quadrivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza viruses is produced and purified separately. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL QUADRIVALENT is a sterile, translucent to whitish opalescent suspension in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon shaking to form a homogeneous suspension.

FLULAVAL QUADRIVALENT has been standardized according to USPHS requirements for the 2013-2014 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 4 viruses (two A strains and two B strains): A/California/7/2009 NYMC X-179A (H1N1), A/Texas/50/2012 NYMC X-223A (H3N2) (an A/Victoria/361/2011-like virus), B/Massachusetts/2/2012 NYMC BX-51B, and B/Brisbane/60/2008.

Thimerosal, a mercury derivative, is added as a preservative. Each 0.5-mL dose contains 50 mcg thimerosal (<25 mcg mercury), α-tocopheryl hydrogen succinate (≤320 mcg), and polysorbate 80 (≤887 mcg). Each 0.5-mL dose may also contain residual amounts of ovalbumin (≤0.3 mcg), formaldehyde (≤25 mcg), and sodium deoxycholate (≤50 mcg) from the manufacturing process. Antibiotics are not used in the manufacture of this vaccine.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Public health authorities recommend influenza vaccine strains annually. Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains representing the influenza viruses likely to circulate in the United States during the influenza season. Two B strain lineages (Victoria and Yamagata) are of public health importance because they have co-circulated since 2001. FLULAVAL (trivalent influenza vaccine) contains only two influenza A subtype viruses and one influenza type B virus. In 6 of the last 11 seasons, the most predominant circulating influenza B lineage was not included in the annual trivalent vaccine. Quadrivalent vaccines, such as FLULAVAL QUADRIVALENT, contain two influenza A subtype viruses and two influenza type B viruses (one of the Victoria lineage and one of the Yamagata lineage).

Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human

challenge studies, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.[1,2] Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine.

Annual revaccination is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.[3]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential. Vaccination of female rats with FLULAVAL QUADRIVALENT, at doses shown to be immunogenic in the rat, had no effect on fertility.

14 CLINICAL STUDIES

14.1 Efficacy Against Influenza

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Study 3, a randomized, observer-blind, non-influenza vaccine-controlled study conducted in 3 countries in Asia, 3 in Latin America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy subjects 3 through 8 years of age were randomized (1:1) to receive FLULAVAL QUADRIVALENT (N = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage) influenza strains, or HAVRIX (N = 2,584), as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX *[see Adverse Reactions (6.1)]*.

Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease presenting as influenza-like illness (ILI). ILI was defined as a temperature ≥100°F in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine efficacy was calculated based on the ATP cohort for efficacy (Table 5).

Table 5. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy Against Influenza A and/or B in Children 3 Through 8 Years of Age[a] (According to Protocol Cohort for Efficacy)

	N[b]	n[c]	Influenza Attack Rate % (n/N)	Vaccine Efficacy % (CI)
All RT-PCR-Positive Influenza				
FLULAVAL QUADRIVALENT	2,379	58	2.4	55.4[d] (95% CI: 39.1, 67.3)
HAVRIX[e]	2,398	128	5.3	–
All Culture-Confirmed Influenza[f]				
FLULAVAL QUADRIVALENT	2,379	50	2.1	55.9 (97.5% CI: 35.4, 69.9)
HAVRIX[e]	2,398	112	4.7	–
Antigenically Matched Culture-Confirmed Influenza				
FLULAVAL QUADRIVALENT	2,379	31	1.3	45.1[g] (97.5% CI: 9.3, 66.8)
HAVRIX[e]	2,398	56	2.3	–

CI = Confidence Interval; RT-PCR = reverse transcriptase polymerase chain reaction.

[a] Study 3: NCT01218308.

[b] According to protocol cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol-specified efficacy criteria.

[c] Number of influenza cases.

[d] Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30% for the lower limit of the 2-sided 95% CI.

[e] Hepatitis A Vaccine used as a control vaccine.

[f] Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with HAVRIX)].

[g] Since only 67% of cases could be typed, the clinical significance of this result is unknown.

In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI was evaluated in subjects 3 through 4 years of age and 5 through 8 years of age; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2), respectively. As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

As a secondary objective in the study, subjects with RT-PCR-positive influenza A and/or

B were prospectively classified based on the presence of adverse outcomes that have been associated with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup and/or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including myositis, encephalitis, seizure and/or myocarditis).

The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction. The incidence of these adverse outcomes is presented in Table 6.

Table 6. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated With RT-PCR-Positive Influenza in Children 3 Through 8 Years of Age[a] (Total Vaccinated Cohort)[b]

	FLULAVAL QUADRIVALENT N = 2,584			HAVRIX[c] N = 2,584		
Adverse Outcome[d]	**Number of Events**	**Number of Subjects[e]**	**%**	**Number of Events**	**Number of Subjects[e]**	**%**
Fever >102.2°F/39.0°C	16[f]	15	0.6	51[f]	50	1.9
Shortness of breath	0	0	0	5	5	0.2
Pneumonia	0	0	0	3	3	0.1
Wheezing	1	1	0	1	1	0
Bronchitis	1	1	0	1	1	0
Pulmonary congestion	0	0	0	1	1	0
Acute otitis media	0	0	0	1	1	0
Bronchiolitis	0	0	0	0	0	0
Croup	0	0	0	0	0	0
Encephalitis	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0
Myositis	0	0	0	0	0	0
Seizure	0	0	0	0	0	0

[a] Study 3: NCT01218308.

[b] Total vaccinated cohort included all vaccinated subjects for whom data were available.

[c] Hepatitis A Vaccine used as a control vaccine.

[d] In subjects who presented with more than one adverse outcome, each outcome was counted in the respective category.

[e] Number of subjects presenting with at least one event in each group.

[f] One subject in each group had sequential influenza due to influenza type A and type B viruses.

14.2 Immunological Evaluation

Adults: Study 1 was a randomized, double-blind, active-controlled, safety and immunogenicity study conducted in subjects 18 years of age and older. In this study, subjects received FLULAVAL QUADRIVALENT (N = 1,246), or one of two formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, N = 204 or TIV-2, N = 211), each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) *[see Adverse Reactions (6.1)]*.

Immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoint was geometric mean antibody titers (GMTs) adjusted for baseline, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (Table 7). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 7).

Table 7. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) 21 Days Post-Vaccination in Adults 18 Years of Age and Older[a] (According to Protocol Cohort for Immunogenicity)[b]

	FLULAVAL QUADRIVALENT[c]	**TIV-1 (B Victoria)[d]**	**TIV-2 (B Yamagata)[e]**
Geometric Mean Titers Against	**N = 1,245-1,246 (95% CI)**	**N = 204 (95% CI)**	**N = 210-211 (95% CI)**
A/California/7/2009 (H1N1)	204.6[f] (190.4, 219.9)	176.0 (149.1, 207.7)	149.0 (122.9, 180.7)
A/Victoria/210/2009 (H3N2)	125.4[f] (117.4, 133.9)	147.5 (124.1, 175.2)	141.0 (118.1, 168.3)
B/Brisbane/60/2008 (Victoria lineage)	177.7[f] (167.8, 188.1)	135.9 (118.1, 156.5)	71.9 (61.3, 84.2)
B/Florida/4/2006 (Yamagata lineage)	399.7[f] (378.1, 422.6)	176.9 (153.8, 203.5)	306.6 (266.2, 353.3)

CI = Confidence Interval.

[a] Study 1: NCT01196975.

[b] According to protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one study vaccine antigen.

[c] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)

[d] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)

[e] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

[f] Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5]; superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV) >1.5].

Children: Study 2 was a randomized, double-blind, active-controlled study conducted in children 3 through 17 years of age. In this study, subjects received FLULAVAL QUADRIVALENT (N = 878), or one of two formulations of a comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 871 or TIV-2 N = 878), each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) *[see Adverse Reactions (6.1)]*.

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days following one or 2 doses of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and seroconversion rates (Table 8). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 8).

Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) at 28 Days Post-Vaccination in Children 3 Through 17 Years of Age[a] (According to Protocol Cohort for Immunogenicity)[b]

	FLULAVAL QUADRIVALENT[c]	TIV-1 (B Victoria)[d]	TIV-2 (B Yamagata)[e]
Geometric Mean Titers Against	**N = 878 (95% CI)**	**N = 871 (95% CI)**	**N = 877-878 (95% CI)**
A/California/7/2009 (H1N1)	362.7[f] (335.3, 392.3)	429.1 (396.5, 464.3)	420.2 (388.8, 454.0)
A/Victoria/210/2009 (H3N2)	143.7[f] (134.2, 153.9)	139.6 (130.5, 149.3)	151.0 (141.0, 161.6)
B/Brisbane/60/2008 (Victoria lineage)	250.5[f] (230.8, 272.0)	245.4 (226.9, 265.4)	68.1 (61.9, 74.9)
B/Florida/4/2006 (Yamagata lineage)	512.5[f] (477.6, 549.9)	197.0 (180.7, 214.8)	579.0 (541.2, 619.3)
Seroconversion[g] to:	**N = 876 % (95% CI)**	**N = 870 % (95% CI)**	**N = 876-877 % (95% CI)**
A/California/7/2009 (H1N1)	84.4[f] (81.8, 86.7)	86.8 (84.3, 89.0)	85.5 (83.0, 87.8)
A/Victoria/210/2009 (H3N2)	70.1[f] (66.9, 73.1)	67.8 (64.6, 70.9)	69.6 (66.5, 72.7)
B/Brisbane/60/2008 (Victoria lineage)	74.5[f] (71.5, 77.4)	71.5 (68.4, 74.5)	29.9 (26.9, 33.1)
B/Florida/4/2006 (Yamagata lineage)	75.2[f] (72.2, 78.1)	41.3 (38.0, 44.6)	73.4 (70.4, 76.3)

CI = Confidence Interval.

[a] Study 2: NCT01198756.

[b] According to protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one study vaccine antigen.

[c] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[d] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

[e] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

[f] Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT ≤10%); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs

[lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV) >1.5] and seroconversion rates (lower limit of the 2-sided 95% CI on difference of FLULAVAL QUADRIVALENT minus the TIV >10%).

[g] Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

15 REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138.
2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777.
3. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(RR-8):1-62.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL QUADRIVALENT is supplied in a 5-mL multi-dose vial containing 10 doses (0.5 mL each).

NDC 19515-895-01 Vial (containing 10 doses) in Package of 1: NDC 19515-895-11

Once entered, a multi-dose vial should be discarded after 28 days. Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLULAVAL QUADRIVALENT.
- Educate regarding potential side effects, emphasizing that (1) FLULAVAL QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and (2) FLULAVAL QUADRIVALENT is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- Instruct to report any adverse events to their healthcare provider.
- Inform that safety and efficacy have not been established in pregnant women. Register women who receive FLULAVAL QUADRIVALENT while pregnant in the pregnancy registry by calling 1-888-452-9622.
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

- Instruct that annual revaccination is recommended.

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